



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US00/03983</p> <p>(22) International Filing Date: 16 February 2000 (16.02.00)</p> <p>(30) Priority Data: 60/128,571 9 April 1999 (09.04.99) US</p> <p>(71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): MAGNUS, Leslie [US/US]; 68 Rockledge Drive, Livingston, NJ 07039 (US). SALTEL, Douglas, A. [CA/US]; 30 Edgemont Avenue, Summit, NJ 07901 (US).</p> <p>(74) Agents: RYAN, M., Andrea; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.</p>	<p>(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
<p>(54) Title: COMBINATIONS OF GABA ANALOGS AND TRICYCLIC COMPOUNDS TO TREAT DEPRESSION</p> <p>(57) Abstract</p> <p>The instant invention is a method of using certain analogs of glutamic acid and gamma-aminobutyric acid in combination with tricyclic compounds to relieve depression.</p>		

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COMBINATIONS OF GABA ANALOGS AND TRICYCLIC COMPOUNDS TO TREAT DEPRESSION

BACKGROUND OF THE INVENTION

1. Field Of The Invention

5 The present invention relates to the use of analogs of glutamic acid and gamma-aminobutyric acid (GABA) in combination with tricyclic compounds for the treatment of depression.

2. Description of Related Art

10 The GABA analogs of the present invention are known agents useful in antiseizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity. It has also been suggested that the compounds can be used as antidepressants, anxiolytics, and antipsychotics. See WO 92/09560 (United States Serial Number 618,692 filed November 27, 1990) and WP 93/23383 (United
15 States Serial Number 886,080 filed May 20, 1992).

 WO 97/33858 teaches that compounds related to gabapentin are useful or treating epilepsy, faintness attacks, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, and
20 neuropathological disorders. WO 97/33858 does not specify what forms of pain are treated.

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Additionally, the compounds of the invention are known for treatment of neuropathic pain. For example, see Rosner H; Rubin L; Kestenbaum A., Gabapentin adjunctive therapy in neuropathic pain states. Clin J Pain, 1996 Mar, 12:1, 56-8; Segal AZ; Rordorf G., Gabapentin as a novel treatment for postherpetic neuralgia. Neurology, 1996 Apr, 46:4, 1175-6; Wetzel CH; Connelly JF., Use of gabapentin in pain management. Ann Pharmacother, 1997 Sep, 31:9, 1082-3; Zapp JJ., Postpoliomyelitis pain treated with gabapentin [letter]. Am Fam Physician, 1996 Jun, 53:8, 2442, 2445; Cheville A, et al., Neuropathic pain in radiation myelopathy: a case report. Program book, American Pain Society (14th Annual Scientific Meeting). Abstract #95823, p. A-115; Sist T; Filadora V; Miner M; Lema M., Gabapentin for idiopathic trigeminal neuralgia: report of two cases. Neurology, 1997 May, 48:5, 1467; Waldman SD, Tutorial 28: Evaluation and Treatment of Trigeminal Neuralgia. Pain Digest (1997) 7:21-24; Mellick LB; Mellick GA., Successful treatment of reflex sympathetic dystrophy with gabapentin [letter]. Am J Emerg Med, 1995 Jan, 13:1, 96; Mellick GA; Seng MI., The use of gabapentin in the treatment of reflex sympathetic dystrophy and a phobic disorder. Am J Pain Manage 1995; 5:7-9; Mellick GA; Mellick LB; Mellick LB., Gabapentin in the management of reflex sympathetic dystrophy [letter]. J Pain Symptom Manage, 1995 May, 10:4, 265-6; Mellick GA; Mellick LB., Reflex sympathetic dystrophy treated with gabapentin. Arch Phys Med Rehabil, 1997 Jan, 78:1, 98-105 and Mackin GA., Medical and pharmacologic management of upper extremity neuropathic pain syndromes. J Hand Ther, 1997

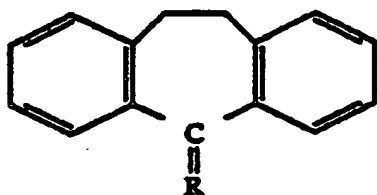
Tricyclic antidepressants are prescribed for endogenous depression, a condition thought to be caused by a defect in the uptake of amine neurotransmitters at the presynaptic junctions. The tricyclic antidepressants benefit from a controlled delivery formulation for a number of reasons. Depressed patients are at a higher risk for suicide, and thus more likely to hoard the drug and then attempt to take an overdose. Furthermore, tricyclic antidepressants have a long induction period, sometimes taking several weeks before patients obtain relief from the drug. As a result of the long induction period, patients often stop using the medication after a short period of time because they think it is not working. A controlled delivery form of the drug solves these problems by providing continuous release of the drug for the time period necessary to provide relief.

Additionally, many patients who respond to tricyclic antidepressants are much more likely to avoid a relapse if they are maintained on the drug. However, patient compliance to long-term drug regimens is generally very poor. This problem is also eliminated with controlled release drug formulations.

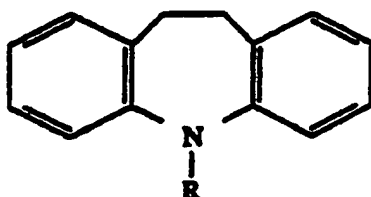
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Representative examples of tricyclic antidepressants are shown below.

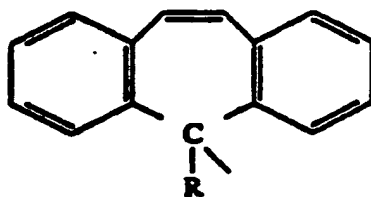
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Tricyclic antidepressant drugs such as imipramine, 2-chloroimipramine and amitriptyline; penfluridol; haloperidol; pimozone; clozapine; calmidazolium; and, mixtures and pharmaceutically acceptable salts of any of the foregoing are useful in the present invention

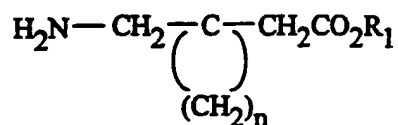
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SUMMARY OF THE INVENTION

The invention related to methods and compositions for treating patients suffering from depression. In methods according to the invention, compositions comprising a gaba analog and a tricyclic antidepressant in a pharmaceutically-acceptable vehicle are administered to a patient suffering from depression. Compositions according to the invention comprise at least one gaba analog and at least one tricyclic antidepressant both in amounts effective to alleviate symptoms of depression.

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This invention provides a method for treating depression comprising administering to a subject suffering from depression an effective amount of a GABA analog in combination with an effective amount of a tricyclic compounds. A preferred embodiment utilizes a cyclic amino acid compound of Formula I



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I

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wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof. An especially preferred embodiment utilizes a compound of Formula I where R_1 is hydrogen and n is 4, which compound is 1-(aminomethyl)-cyclohexane acetic acid, known generically as gabapentin.

In another embodiment, the invention includes treating depression with a compound of Formula II.

Formula II



or a pharmaceutically acceptable salt thereof wherein

R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl; and tricyclic compounds.

Preferred compounds of the invention are those wherein R_3 and R_2 are hydrogen, and R_1 is $-(CH_2)_{0-2}-i$ C_4H_9 as an (R), (S), or (R,S) isomer.

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The more preferred compounds of Formula II invention are (S)-3-(aminomethyl)-5-methylhexanoic acid and 3-aminomethyl-5-methyl-hexanoic acid, now known generically as pregabalin.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

5 The method of this invention utilizes any GABA analog. A GABA analog is any compound derived from or based upon gamma-aminobutyric acid. The compounds are readily available, either commercially, or by synthetic methodology well-known to those skilled in the art of organic chemistry. The preferred GABA analogs to be utilized in the method of this invention are cyclic
10 amino acids of Formula I. These are described in U.S. Patent 4,024,175, which is incorporated herein by reference. Another preferred method utilizes the GABA analogs of Formula II, and these are described in U.S. Patent 5,563,175, which is incorporated herein by reference.

15 All that is required to practice the method of this invention is to administer a GABA analog in combination with tricyclic compounds. The amount of GABA analog in the composition will generally be from about 1 to about 300 mg per kg of subject body weight. Typical doses will be from about 10 to about 5000 mg per day for an adult subject of normal weight. It is expected that common doses that
20 might be administered could be from 100 mg three times a day up to 600 mg four times a day. Commercially available capsules of 100 mg, 300 mg, and 400 mg of gabapentin can be administered. Alternate forms include liquids and film-coated

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tablets.

If a compound of Formula II, such as pregabalin is used, the dosage level is one sixth that of gabapentin. The dosage range for pregabalin is from about 0.15 mg to about 50 mg per kg per day of subject body weight. Typical dosages for pregabalin will be from about 1.6 mg to about 840 mg per day with individual dosages ranging from about 0.15 mg to about 65 mg per dose.

The dosage range for the tricyclic antidepressant can be determined by one skilled in the art. Amitriptyline is available in 10, 25, 50, 75 and 150 mg tablets. Daily dosages can range from between 75 to 350 mg.

A benefit of the claimed compositions is to lessen the chance of overdose. Overdoses of antidepressants are common reports to poison control centers. As a result, physicians and pharmacists are encouraged to provide small prescriptions (2 to 4 weeks) at a time to avoid providing a potential suicide victim with the tools to do it. Antidepressants are therefore potentially lethal as the dose is increased and patients have to be titrated up to an effective dose.

This invention would allow for a synergistic improvement in mood with lower doses (therefore) safer and potentially faster. The different mechanism of action of the two drugs would offer greater benefit to patients.

The compounds of the present invention may form pharmaceutically acceptable salts with both organic and inorganic acids or bases. For example, the

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acid addition salts of the basic compounds are prepared either by dissolving the free base in aqueous or aqueous alcohol solution or other suitable solvents containing the appropriate acid and isolating the salt by evaporating the solution. Examples of pharmaceutically acceptable salts are hydrochlorides, hydrobromides, hydrosulfates, etc. as well as sodium, potassium, and magnesium, etc. salts.

The compounds of the Formula II can contain one or several asymmetric carbon atoms. The invention includes the individual diastereomers or enantiomers, and the mixtures thereof. The individual diastereomers or enantiomers may be prepared or isolated by methods already well-known in the art.

Formulating the active compound in dosage unit form with a pharmaceutical carrier produces pharmaceutical compositions of the compound of the present invention or its salts. Some examples of dosage unit forms are tablets, capsules, pills, powders, aqueous and nonaqueous oral solutions and suspensions, and parenteral solutions packaged in containers containing either one or some larger number of dosage units and capable of being subdivided into individual doses.

Some examples of suitable pharmaceutical carriers, including pharmaceutical diluents, are gelatin capsules; sugars such as lactose and sucrose; starches such as corn starch and potato starch, cellulose derivatives such as sodium carboxymethyl cellulose, ethyl cellulose, methyl cellulose, and cellulose

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acetate phthalate; gelatin; talc; stearic acid; magnesium stearate; vegetable oils such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil, and oil of theobroma; propylene glycol, glycerin; sorbitol; polyethylene glycol; water; agar; alginic acid; isotonic saline, and phosphate buffer solutions; as well as other compatible substances normally used in pharmaceutical formulations. The compositions of the invention can also contain other components such as coloring agents, flavoring agents, and/or preservatives. These materials, if present, are usually used in relatively small amounts. The compositions can, if desired, also contain other therapeutic agents.

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The percentage of the active ingredients in the foregoing compositions can be varied within wide limits, but for practical purposes it is preferably present in a concentration of at least 10% in a solid composition and at least 2% in a primary liquid composition. The most satisfactory compositions are those in which a much higher proportion of the active ingredient is present.

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Routes of administration of the subject compound or its salts are oral or parenteral. For example, a useful intravenous dose is between 5 and 50 mg and a useful oral dosage is between 20 and 800 mg. The dosage is within the dosing range used in treatment of pain or as would be with the needs of the patient as described by the physician.

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The advantages of using the compounds of Formula I and II, especially

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gabapentin and pregabalin, in the instant invention include the relatively nontoxic nature of the compounds, the ease of preparation, the fact that the compounds are well-tolerated, and the ease of IV administration of the drugs. Gabapentin has few interactions with major classes of drugs since it is not metabolized in the liver, but rather excreted unchanged from the body. Further, the drugs are not metabolized in the body. The subjects treated with the method of the present invention are mammals, including humans.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

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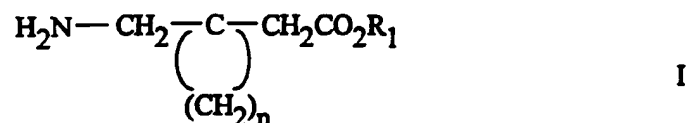
What is claimed is:

1. A method for treating a patient having depression comprising administering a pharmaceutical composition comprising:

(a) a therapeutically effective amount of a GABA analog; and

5 (b) a therapeutically effective amount of a tricyclic compounds.

2. The method according to claim 1, wherein the GABA analog is the compound according to Formula I:



10 wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

3. The method according to claim 2, wherein Formula I comprises gabapentin.

15

4. The method according to claim 2, comprising from about 10 mg to about 400 mg of Formula I.

5. The method according to claim 3, comprising from about 10 mg to
20 about 400 mg of gabapentin.

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6. The method according to claim 3, comprising from about 10 mg to about 400 mg of gabapentin and from about 25 mg to about 350 mg of tricyclic antidepressant.

7. The method according to claim 1, wherein the GABA analog is a compound according to Formula II:



or a pharmaceutically acceptable salt thereof wherein

R₁ is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or cycloalkyl of from 3 to 6 carbon atoms;

R₂ is hydrogen or methyl; and

R₃ is hydrogen, methyl, or carboxyl.

8. The method according to claim 7, wherein Formula II comprises pregabalin.

9. The method according to claim 7, comprising from about .15 mg to about 65 mg of Formula II.

10. The method according to claim 8, comprising from about .15 mg to about 65 mg of pregabalin.

11. A composition for treating depression in a human comprising:

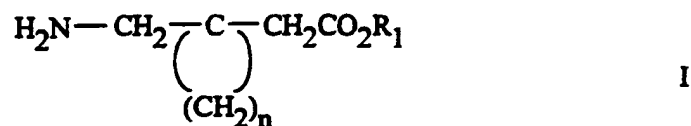
(a) a therapeutically effective amount of a GABA analog; and

(b) a therapeutically effective amount of a tricyclic compounds.

12. The composition according to claim 11, wherein the GABA analog

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the compound according to Formula I:



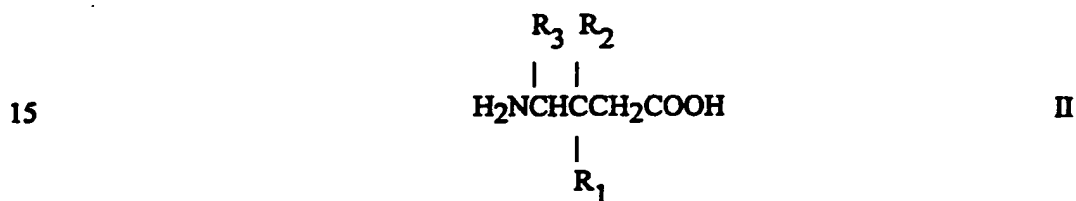
wherein R_1 is hydrogen or lower alkyl and n is an integer of from 4 to 6, and the pharmaceutically acceptable salts thereof.

5 13. The composition method according to claim 12, wherein Formula I comprises gabapentin.

 14. The composition according to claim 12, comprising from about 10 mg to about 400 mg of Formula I.

 15. The composition according to claim 13, comprising from about 10
10 mg to about 400 mg of gabapentin.

 16. The composition according to claim 11, wherein the GABA analog is a compound according to Formula II:



or a pharmaceutically acceptable salt thereof wherein

R_1 is a straight or branched alkyl of from 1 to 6 carbon atoms, phenyl, or

20 cycloalkyl of from 3 to 6 carbon atoms;

R_2 is hydrogen or methyl; and

R_3 is hydrogen, methyl, or carboxyl.

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17. The composition according to claim 16, wherein Formula II comprises pregabalin.

18. The composition according to claim 16, comprising from about .15 mg to about 65 mg of Formula II.

5 19. The composition according to claim 18, comprising from about .15 mg to about 65 mg of pregabalin.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/03983

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P25/24 A61K45/06 A61K31/645 A61K31/55 A61K31/445
A61K31/415 //(A61K31/645,31:195),(A61K31/55,31:195),
(A61K31/445,31:195),(A61K31/415,31:195)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FR 2 262 997 A (HOECHST AG) 3 October 1975 (1975-10-03) page 2, line 17-21; claims 1,2	1, 11
X	WETZEL C H ET AL: "Use of gabapentin in pain management" ANNALS OF PHARMACOTHERAPY, XX, XX, vol. 31, no. 9, September 1997 (1997-09), pages 1082-1083, XP002101739 ISSN: 1060-0280	11-15
A	page 1083, left-hand column --- -/-	1-6



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
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- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "Z" document member of the same patent family

Date of the actual completion of the international search

3 August 2000

Date of mailing of the international search report

10/08/2000

Name and mailing address of the ISA

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Kanbier, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/03983

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SABETKASAI, M. ET AL: "Baclofen and antidepressant -induced antinociception in formalin test: possible GABAB mechanism involvement" PSYCHOPHARMACOLOGY (BERLIN) (1999), 142(4), 426-431 , XP000933550 page 429-430; figure 3	1,11
X	EP 0 726 073 A (BLEIWEISS DANIEL GUSTAVO) 14 August 1996 (1996-08-14) column 2, line 2-15; claims 1-7 column 12, line 10-25	11
X	FR 2 453 643 A (SYNTHELABO) 7 November 1980 (1980-11-07) page 4, line 25-31; claims page 8, line 10-15	11
A	US 5 025 035 A (WARNER-LAMBERT COMPANY) 18 June 1991 (1991-06-18) claims	1-6, 11-15
A	WO 92 09560 A (UNIV NORTHWESTERN) 11 June 1992 (1992-06-11) cited in the application page 1, line 13,14; table 1 page 4, line 14-25 page 9, line 18,19	1-3,7, 11-13,16

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box 1.2

Present claims 1-19 relate to methods and compositions involving an extremely large number of possible compounds, by way of the terms "GABA analog" and "tricyclic compounds". Due thereto, a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of complete scope of the claims impossible.

Furthermore, the claims also relate to methods and compositions involving compounds defined by reference to a desirable characteristic or property, namely antidepressant activity of the compound in question. The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). A compound is not sufficiently defined by its mechanism of action and/or pharmacological profile. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, concise, supported and disclosed, namely those parts relating methods and compositions involving compounds specifically mentioned in claims 2-10 and 12-19, with due regard to the description insofar as specific tricyclic/antidepressant compounds are mentioned, and the general idea underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. l. Application No

PCT/US 00/03983

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